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Proteomics profiling reveals inflammatory biomarkers of antidepressant treatment response: Findings from the CO-MED trial

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ABSTRACT

Animal and human studies suggest an association between depression and aberrant immune response. Further, common inflammatory markers may change during the course of antidepressant treatment in patients. The objective of this study was to evaluate changes in inflammatory markers and clinical outcomes from subjects enrolled in the Combining Medications to Enhance Depression Outcome (CO-MED) trial. At baseline and week 12 (treatment completion), plasma samples of 102 participants were analyzed via a multiplex assay comprised of inflammatory markers using a 27-plex standard assay panel plus a 4-plex human acute phase xMAP technology based platform. We carried out analyses in two steps. First, t-tests were used to identify inflammatory marker levels that changed between baseline and week 12. For markers that were altered, logistic regression models were then conducted to look for associated changes in remission at week 12. Among the 31 inflammatory markers analyzed, several cytokines (IL-5, IFN-γ, IL-13), two chemokines (Eotaxin-1/CCL11, RANTES) and an acute-phase reactant (serum amyloid P component) showed change from baseline to week 12. However, only two indicated differential remission responses. Interestingly, increased levels of Eotaxin-1/CCL11 correlated with remission at week 12, whereas decreased levels of IFN-γ correlated with non-remission at week 12. Results suggest that these inflammatory proteins may serve as predictors of treatment response.

1. Introduction

A state of sub-threshold systemic inflammation has been implicated in the pathophysiology of Major Depressive Disorder (MDD) (Dantzer et al., 2008; Felger and Lotrich, 2013), while few studies show specific changes in inflammatory biomarkers with antidepressant treatment. Several reports demonstrate that MDD patients, as compared to healthy controls, have elevated levels of inflammatory cytokines during depressive episodes, including interleukin (IL) −1, IL-6, IL-8, IL-10, interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNFα) (Kenis and Maes, 2002; Maes et al., 1999; Munzer et al., 2013). The association of MDD with inflammation is also supported by the fact that IFN treatment of hepatitis C and certain types of cancers frequently induces depressive symptoms (Hauser et al., 2002). Grassi-Oliveira and colleagues have also reported that levels of certain chemokines (monocyte chemoattractant protein-1 [MCP-1/CCL-2] and RANTES/CCL5) are lower in serum samples from adults with MDD and suicidal ideation as compared to controls, whereas higher levels of Eotaxin-1/CCL-11 (further referred to as Eotaxin-1) are seen in those with MDD and suicidal ideation (Grassi-Oliveira et al., 2012), although neither study assessed changes with treatment.

Inflammatory markers have also been examined as predictors and moderators of treatment response in depression. Brunoni and colleagues showed that IL-2, IL-4, and IL-17 (but not TNFα) decreased over 6 weeks of treatment with transcranial direct current stimulation (tDCS) and/or sertraline in MDD patients, independent of treatment response (Brunoni et al., 2014). Similarly, tricyclic antidepressants (TCAs) have been shown to decrease IFN-γ, IL-17, IL-22 (Himmerich et al., 2010a, 2010b). In the Genome-Based Therapeutic Drugs for Depression (GENDEP) study, baseline C-reactive protein (CRP), a biomarker for systemic inflammation,

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predicted differential response to two different treatments. Specifically, lower levels of CRP were associated with improved response with escitalopram, while higher levels of CRP were associated with improved response to nortriptyline (Uher et al., 2014). Similar results were seen in the Combining Medications to Enhance Depression Outcomes (CO-MED) trial, which showed that higher baseline CRP levels were associated with better responsiveness to bupropion-SSRI combination, as compared to SSRI monotherapy (Jha et al., 2017). Further, combinations of antidepressants and anti-inflammatory drugs like fluoxetine, a selective serotonin reuptake inhibitor (SSRI), and celecoxib (Cyclooxygenase-2, COX-2 inhibitor) have also been associated with a greater antidepressant effect than fluoxetine (Akhondzadeh et al., 2009).

While recent attention has focused on a systemic inflammatory state, there is evidence that some depressed participants have a suppressed immune response (Maes, 1995). Pertinent to our study, cytokines have been analyzed for depression but have not been measured concurrently with acute-phase reactants that serve as markers for a systemic inflammatory state. Recent advances in non-invasive multiplex proteomic xMAP technology platforms can be utilized to quantitatively measure multiple (rather than single) inflammatory markers that may be associated with treatment outcomes (Bot et al., 2015; Stelzhammer et al., 2014).

Here, we used an unbiased and non-targeted exploratory approach to measure baseline to exit levels of a variety of inflammatory markers, including cytokines, chemokines, growth factors and acute-phase reactants in plasma samples from participants of the CO-MED trial, which compared three treatment groups: monotherapy with selective serotonin reuptake inhibitor (SSRI) (escitalopram plus placebo) versus one of two combination therapies: bupropion plus escitalopram (bupropion-SSRI) and venlafaxine plus mirtazapine (venlafaxine-mirtazapine) (Rush et al., 2011). As the three treatment arms did not differ in rates of clinical improvement solely based on symptoms during the CO-MED trial, we combined the three treatment arms for this analysis. Considering the strong link between inflammation and depression and its effect on response to antidepressant treatment, we postulated that antidepressant medications may not only act by inhibiting the reuptake of serotonergic or norepinephrine neurotransmitters, but also by altering the inflammatory response as reflected by change in the levels of inflammatory biomarkers.

2. Methods

2.1. Study overview

The CO-MED trial is a single-blind, randomized, placebo-controlled trial with 665 participants for first-step MDD treatment, including an acute (12 weeks) and long-term continuation (additional 4 months) phase. Randomization was stratified by clinical sites and participants were assigned to one of the three treatment groups (SSRI monotherapy, bupropion-SSRI combination, and venlafaxine-mirtazapine combination) in a 1:1:1 ratio. Study visits were conducted at baseline and weeks 1, 2, 4, 6, 8, 10, 12 for the acute phase. At each visit, study physicians used measurement based care (MBC) for dosage adjustments based on the scores of the Quick Inventory of Depressive Symptoms-Clinician Rated scale (QIDS-C) and Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) scale. The QIDS-C items were extracted from Inventory of Depressive Symptomatology – Clinician-Rated (IDS-C) scale. Clinical outcomes were determined by the Quick Inventory of Depressive Symptoms Self-Report version (QIDS-SR). Plasma was collected at baseline at week 12 (exit) in a subset of patients.

2.2. Study participants

Broad inclusion and minimal exclusion criteria were used to ensure reasonably representative subject groups. Depressed outpatients seeking treatment at participating clinical sites and planning to continue living in the area of that clinical site for the duration of the study were eligible to enroll in the study. These sites included both primary and psychiatric care clinics, and were selected to ensure adequate minority representation. To be included in the study, participants had to meet clinical criteria for nonpsychotic, recurrent (greater than 1 previous episode) or chronic (current episode greater than 2 years) MDD as defined by a clinical interview and confirmed by the MINI International Neuropsychiatric Interview (MINI). Participants had to have at least 2 months duration of the current depressive episode and score 16 or greater on the 17-item Hamilton Rating Scale. Exclusion criteria for this clinical trial are fully listed on the clinicaltrials.gov website (https://clinicaltrials.gov/ct2/show/NCT00590863).

These studies were carried out in accordance with the latest version of the Declaration of Helsinki. The Institutional Review Boards at UT Southwestern Medical Center at Dallas, the University of Pittsburgh Data Coordinating Center, each participating regional center, and all relevant clinical sites reviewed and approved the study protocol, all consent documents, and study procedures. All participants were informed of the study in detail, including risks and benefits, and provided written informed consent prior to completing any study procedures. An independent data safety and monitoring board also monitored the study. Further details of CO-MED trial have been described by Rush et al. (2011).

A subgroup of 102 participants (out of the total 665 enrolled in the CO-MED trial) provided plasma samples at both baseline and week 12 and were used for these analyses.

Antidepressant medications: Participants in all three treatment groups received two types of pills. The first medication was known to both participants and study personnel, while the second medication was known only to study personnel. All dose adjustments were based on clinical response and tolerability according to the principles of MBC (Trivedi et al., 2006).

Participants in the SSRI monotherapy treatment group were started on 10 mg/day dose of escitalopram with the option to increase the dose to 20 mg/day at week 4 visit or later if QIDS-C score was greater than 5. Pill placebo was added at week 2 in single-blind fashion with the option to increase the dose at week 4 visit or later if QIDS-C score was greater than 5. At the end of 12 weeks, mean escitalopram dose was 17.6 mg/day and mean placebo dose was 1.4 pills/day. Participants in the Bupropion-SSRI treatment group were started on sustained release (SR) bupropion 150 mg/day and the dose was increased to 300 mg/day at week 1 visit. At week 2, escitalopram 10 mg/day was started in single-blind fashion. At week 4 visit, bupropion SR was increased to 400 mg/day and/or escitalopram was increased to 20 mg/day if QIDS-C score was greater than 5. For visits at week 6 and later, doses could be increased to 400 mg/day of bupropion SR and 20 mg/day of escitalopram if QIDS-C score was greater than 5. At the end of 12 weeks, mean bupropion SR dose was 324.0 mg/day and mean escitalopram dose was 14.0 mg/day. Participants in venlafaxine-mirtazapine combination treatment group were started on extended release (XR) venlafaxine 37.5 mg/day for 3 days and then increased to 75 mg/day. At week 1 visit, venlafaxine XR was increased to 150 mg/day. At week 2 visit, if the score on QIDS-C was greater than 5 then mirtazapine 15 mg/day was added in single-blind fashion. At week 4 visit, if QIDS-C was greater than 5 then venlafaxine XR dose was increased to 225 mg/day and/or mirtazapine was increased to 30 mg/day. At week 6, if QIDS-C was greater than 5 then mirtazapine could be raised to 45 mg/day. At week 8, if QIDS was greater